American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:191–196 (1996)

Unique Case of Growth Hormone (GH) Deficiency Accompanied by Clinical Anophthalmia, Hypoplastic Orbits, Digital Dysplasia, Short Stature, Obesity, and Diabetes Mellitus

Kimiko Ishikawa, Motoi Sohmiya, Satoshi Ohguni, Toshiaki Sato, Keiichiro Tanigawa, and Yuzuru Kato

First Division, Department of Medicine, Shimane Medical University, Izumo, Japan

A 43-year-old female was admitted to our hospital for polydipsia and hyperglycemia. She had total blindness and globes were not recognized by inspection, indicating clinical anophthalmia. Physical examination revealed short stature, obesity, prematurely gray hair, shortness of fingers and toes, syndactyly, and multiple dental caries. Laboratory examination showed hyperglycemia, increased glycosilated hemoglobin (HbA_1c) and insulin resistance on euglycemic glucose clamp. Blunted growth hormone (GH) secretion was shown in response to insulin-induced hypoglycemia, arginine infusion, and GH-releasing hormone (GHRH) loading test, and in 24 h spontaneous GH profile. Magnetic resonance imaging (MRI) and computed tomography (CT) showed dysostosis of orbit, defect of optic nerve, enlarged suprasellar cistern, and prolonged pituitary stalk. This may be the first report of a unique case with GH deficiency accompanied by clinical anophthalmia, hypoplastic orbits, digital dysplasia, short stature, obesity, and diabetes mellitus.

KEY WORDS: GH deficiency, clinical anophthalmia, congenital anomaly, diabetes mellitus, insulin resistance

INTRODUCTION

Clinical anophthalmia is one of the rare congenital anomalies [Amemiya and Nishimura, 1977a; McIntosh et al., 1954; Neel, 1958]. The frequency of anophthalmia and microphthalmia is 0.009 to 0.012% of total deliveries. Congenital GH deficiency is mostly idiopathic and may be associated with developmental abnormalities. GH secretion is rarely impaired in such congenital anomalies as primordial dwarfism [Imura et al., 1974] and Turner's syndrome [Reiter et al., 1991]. In totally blind subjects, spontaneous GH secretion related to sleep-wake cycles may be partly impaired but GH response to provocative stimuli is preserved [Bellastella et al., 1977]. There have been no reports on clinical anophthalmia associated with GH deficiency. In the present study, we report the first unique case of GH deficiency accompanied by clinical anophthalmia, hypoplastic orbits, digital dysplasia, prematurely gray hair, obesity, and diabetes mellitus.

CASE REPORT

A 43-year-old woman was admitted to our hospital because of polydipsia. She was born at full term and normal vaginal delivery after uncomplicated pregnancy. There was no history of maternal exposure to excessive radiation or other teratogen during pregnancy. Her body weight and height were normal at birth. She had total blindness from birth and her globes were not recognized by inspection, indicating clinical anophthalmia. She had syndactyly and her left fifth toe was resected in childhood. Retarded growth was prominent at age 7 when her height was 100 cm, more than 3 SD below the mean for age. Without any medication, her height increased to reach the final height of 135.5 cm at age 15. Her sexual development was normal with menarche at age 13 although her menstrual cycle was rather irregular. She was married but had no children.

In 1994, she consulted a doctor for itching on the genitals and was found to have hyperglycemia of 290 mg/dl. When she was referred to our hospital, plasma glucose was 341 mg/dl, and glycosilated hemoglobin

Received for publication May 12, 1995; revision received October 2, 1995.

Address reprint requests to Dr. Motoi Sohmiya, First Division, Department of Medicine, Shimane Medical University, Izumo 693, Japan.

(HbA_1c) was 9.1%. She complained of polydipsia, polyuria, and numbness of the foot at admission.

Family History

Her parents were intermarried and her mother was 140 cm in height. Her father was killed in action and her mother died at age 73 from gastric cancer. The patient had four brothers, three of which died in childhood from infectious diseases. The youngest brother was alive but he became blind in childhood by unknown cause and his height was 150 cm.

Physical Findings

The patient was 135.5 cm in height and 48.5 kg in weight with body mass index of 27.0 kg/m^2. Body temperature was 35.8°C. The pulse rate was 64/min. The blood pressure was 125/90 mm Hg. General adiposis was recognized as shown in Figure 1. She had total blindness and her globes were not recognized by inspection. The width of palpebral fissure was short (right 11 × 1 mm, left 11 × 1 mm) and there was intermarginal fusion in the auris side. There were many canities in hair. The head was large with the bulging forehead compared to the face and the head circumference was 52 cm. Many caries were recognized and most teeth were fallen out. The chest and the abdomen were intact. As shown in Figure 2, bilateral fifth fingers and bilateral toes except the first toe were short. The left fifth toe was absent after resection.

Laboratory Findings

Laboratory findings on admission are shown in Table I. Plasma glucose levels and HbA_1c were elevated. Serum insulin and urine C-peptide immunoreactivity (CPR) were within the normal range; 75 g oral glucose tolerance test (GTT) indicated diabetic glucose pattern with blunted insulin response. Insulin binding ability to red blood cells was normal, and anti-insulin antibody was not detected in serum. A large quantity of insulin (0.6 U/kg, iv) was required to induce hypoglycemia in insulin tolerance test (ITT). A markedly reduced glucose infusion rate (GIR) of 1.89 mg/kg/min was revealed on euglycemic glucose clamp performed by the method of DeFronzo et al. [1979] at the constant insulin infusion rate of 40 mIU/m^2/min, indicating insulin resistance in the patient. After a loss of 3 kg in body weight and control of plasma glucose with a small amount of insulin (8–10 IU/day), GIR was slightly improved to 3.93 mg/kg/min which remained less than the normal range (5.76–11.12 mg/kg/min) [Ohguni et al., 1995]. Serum cholesterol, triglyceride, and CBC were normal.

Endocrinological loading tests were performed after plasma glucose was well controlled. Plasma GH did not increase in response to insulin-induced hypoglycemia, arginine infusion (30 g for 30 min, iv), or GH-releasing hormone (GH-RH 100 μg, iv) loading test. When spontaneous GH secretion was evaluated by blood sampling every 20 min for 24 h, mean plasma GH value was lowered (1.01 ng/ml vs. normal adults 1.6–5.8 ng/ml). Urinary GH was not detectable. In contrast, plasma TSH, LH, and FSH were well responded to TRH and LHRH loading tests. Plasma arginine vasopressin (AVP) concentration was normal. Serum tri-iodothyronine, thyroxine, cortisol, and urinary 17-OHCS were normal. Plasma cortisol increased in response to insulin-induced hypoglycemia.

Chromosomal analysis showed normal pattern of 46XX.

Diagnostic Imaging Studies

Radiography showed hypoplastic orbit, dysostosis of maxilla, fusion of the right fourth and fifth metacarpal bone at base, short middle phalanx in the bilateral fifth

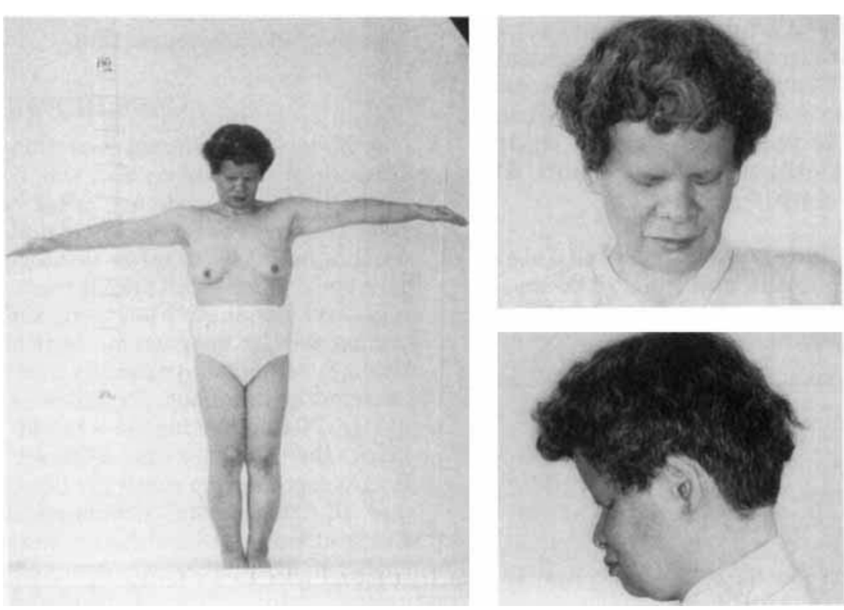

Fig. 1. Photography of the whole body (**left**) and the face (**right**) of the present case, which is characterized by short stature and obesity. Globes were not recognized by inspection. The width of palpebral fissure was small. There was intermarginal fusion in the auris side. The head was large with bulging forehead.

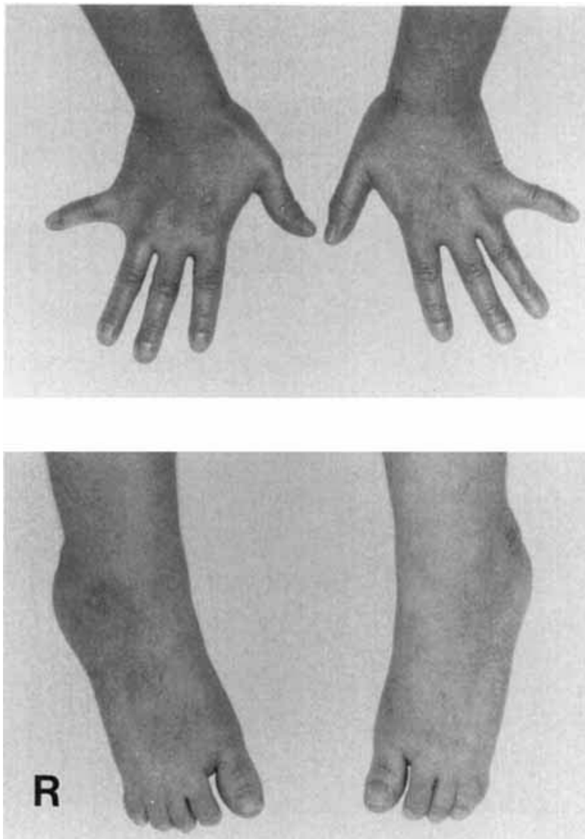

Fig. 2. Photography of the hands (**upper**) and foot (**lower**) of the present case. Bilateral fifth fingers and bilateral toes except the first toe were short. The left fifth toe was resected.

fingers, and thick and extrusion of metatarsal and proximal bone (Figs. 3, 4). Magnetic resonance imaging (MRI) showed that globes and optic nerve were not recognized and that the muscle was little visible in intraorbital fat tissue (Figs. 5–7). The pituitary stalk was prolonged and suprasellar cistern was wide. The upper part of the pituitary stalk was enhanced by Gadolinium diethylenetriam:penta-acetic acid (Gd-DTPA).

DISCUSSION

This is the first report of a unique case of GH deficiency accompanied with a number of such congenital anomalies as anophthalmia, dysostosis of orbit, digital dysplasia and prematurely gray hair, obesity, and insulin-resistant diabetes mellitus. True form of anophthalmia is rare and some intraorbital representation of neuroectodermal structures have been shown in the orbital lesion of most cases with clinical anophthalmia [Brunquell et al., 1984]. Since organogenesis of globes occurs in the fetus at 3 to 12 weeks [Amemiya and Nishimura, 1997a,b; Verloes, 1989], anophthalmia may be caused by some environmental and/or genetic factors in this period. However, detailed history taking failed to find any history of such teratogenic exposure as irradiation, hypoxia, syphilis, rubella, toxoplasmosis, vitamin A deficiency, trauma, and chemicals. There are some genetic factors in this case since her parents were cousins and her youngest brother was suffered from unilateral blindness in childhood.

It is known that anophthalmia or microphthalmia is accompanied by a number of developmental abnormalities. A rare case of microphthalmia or anophthalmia accompanied by X-linked recessive inheritance, mental

TABLE I. Laboratory Data on Admission*

Blood chemistry					
Cholesterol	220 mg/dl (11–240)		Triglycerides	110 mg/dl (55–180)	
HDL-cholesterol	56 mg/dl (28–70)		NEFA	0.55 mEq/L (0.20–0.60)	
Glucose	106 mg/dl (60–100)		HbA_1c	7.3% (3.8–6.0)	
Specific ^{125}I-insulin binding to RBC	5.9% (3.0–8.5)				
Anti-insulin antibody in serum	5.2% (less than 7.0)				
75 g oral glucose tolerance test (OGTT)					
Time (min)	0	30	60	90	120
Plasma glucose mg/dl)	141	232	309	346	368
Serum insulin (U/ml)	6	18	26	35	41
Endocrinology					
Basal GH	0.5 ng/ml (less than 5)		T_3	122 ng/ml (90–195)	
Mean 24-h GH	1.01 ng/ml (1.6–5.8)		T_4	7.3 μg/dl (5.4–13.5)	
IGF-I	110 ng/ml (130.9–267.1)		Free T_4	1.3 ng/ml (0.9–1.9)	
ACTH	19 pg/ml (less than 6)		LH	4.1 mIU/ml (1.4–7.4)	
Cortisol	10 μg/dl (2–18)		FSH	8.4 mIU/ml (3.0–10.2)	
u-17-OHCS	6.8 mg/day (1.9–6.1)		u-C peptide	87.3 μg/day (35–145)	
u-17-KS	3.8 mg/day (3.1–8.8)		u-GH	3.0 ng/day (7–20)	
Stimulation test					
Stimuli	Hormones		Basal	Maximum response	
Insulin (0.6 U/kg, iv)	Glucose		108 mg/dl	50 mg/dl	
	GH		1.1 ng/ml	2.5 ng/ml (more than 7.0)	
Arginine (30 g, iv)	GH		1.2 ng/ml	4.3 ng/ml (more than 7.0)	
GH-RH (100 μg, iv)	GH		0.6 ng/ml	2.8 ng/ml (more than 7.0)	
TRH (500 μg, iv)	TSH		2.1 μU/ml	15.8 μU/ml (8–22)	
	PRL		5.8 ng/ml	66.9 ng/ml (30.2–64.8)	
Chromosome analysis 46XX: normal karyotype					

*( ), normal range; NEFA, nonesterified fatty acid; u-, urinary; PRL, prolactin.

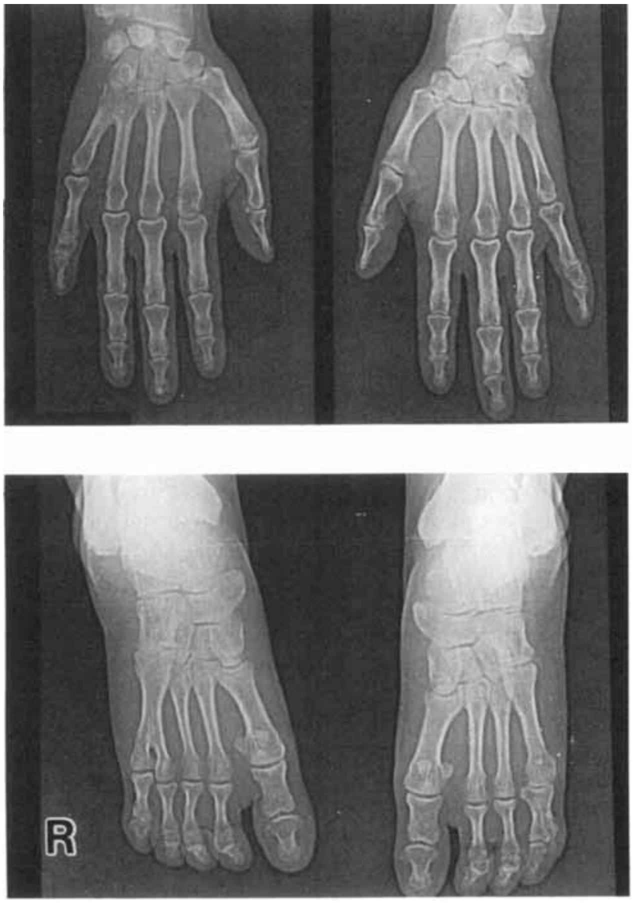

Fig. 3. X-ray photography of the hands (**upper**) and the foot (**lower**) of the present case. Bilateral fifth middle phalanx are short. The left fifth metatarsal bone is absent, and the fifth metatarsal bone and the proximal bone are thick. Extrusion of bone is recognized. The syndactyly of the right fourth and the fifth metatarsal bone at base and at body is shown.

Fig. 4. X-ray photography of the head and the face of the present case. The orbital region is hypoplastic and the dysostosis of the maxilla is evident.

retardation, and fusion anomalies is known as Lenz microphthalmic syndrome or Lenz dysplasia [Lenz, 1955; Traboulsi et al., 1988]. Oculodentodigital dysplasia syndrome is characterized by ocular anomalies including microphthalmia, hypotelorism, irridic changes, syndactyly and camptodactyly of fingers, hypoplasia of the middle phalanges and toe, and hypoplasia of the enamel of teeth [Gorlin et al., 1963; Judisch et al., 1979]. Oculodigital dysplasia is characterized by combination of digital hypoplasia and eye anomalies [Chemke et al., 1978]. Waardenburgs anophthalmia syndrome is accompanied by mental retardation [Traboulsi et al., 1984]. GOMBO syndrome is associated with growth retardation, ocular abnormalities, microcephaly, brachycephaly and oligophrenia [Verloes, 1989]. Kenny syndrome is associated with dwarfism, medullary stenosis, ophthalmologic abnormalities, and transient hypocalcemia [Fernandez et al., 1992]; 13-trisomy is known as dwarfism accompanied by microphthalmia. None of these syndromes are adopted to the present case.

MRI findings such as prolonged pituitary stalk, wide suprasellar cistern, optic nerve defect, narrow orbit, and dysostosis of orbit were not previously reported in pituitary dwarfism [Fujisawa et al., 1987], although endocrinological findings indicated isolated GH deficiency in the present study. Blunted GH secretion in this case

Fig. 5. CT scan of orbital region of the present case. Globes are not recognized.

could not be explained by poorly controlled diabetes or obesity, since the loading test and 24 h blood sampling were performed when fasting plasma glucose levels

Fig. 6. T_1 enhanced MRI of orbital region of the present case. Orbit is filled with fat tissues. Globes are not recognized but there is remnant of eye muscles in the orbit.

were maintained between 101 mg/dl and 131 mg/dl, and $HbA_{1}c$ decreased from 7.1% to 6.5%. Body weight was reduced by diet and body mass index was within the normal range at the examination period. It was also reported that endogenous GH secretion was not suppressed by hyperglycemia in diabetic patients [Kinsley et al., 1995]. Although insulin-induced hypoglycemia was not so remarkable in the present study, GH secretion may be markedly stimulated by a fall in blood glucose without hypoglycemia in diabetic patients [Roth et al., 1964].

It is interesting that obesity and diabetes mellitus were accompanied in this case. Werner's syndrome is accompanied by a part of similar clinical signs and insulin-resistant diabetes mellitus, which was characterized by hyperinsulinemia [Okamoto et al., 1992] and post-insulin receptor abnormality [Yamasaki et al., 1992]. In the present case, a large quantity of insulin (6 U) was required to reduce plasma glucose less than 50 mg/dl on ITT and GIR was very low on glucose clamp study. The constant insulin infusion rate of 40 mIU/m^2/min during euglycemic glucose clamp is enough to suppress hepatic glucose production [DeFronzo et al., 1979; Ohguni et al., 1995]. However, insulin resistance was shortly improved by reducing body weight of 3 kg and a short period of insulin therapy at low doses (8–10 U/day). Although we previously reported that GIR is changed by menstrual cycles in women [Ohguni et al., 1995], the change in insulin resistance was not explained by sex steroid levels in this case. Therefore, insulin resistance in this case could be partly due to obesity and poor control of glucose rather than congenital anomaly in insulin receptor of post-insulin receptor functions.

In summary, this is a unique case of GH deficiency accompanied by clinical anophthalmia, hypoplastic or-

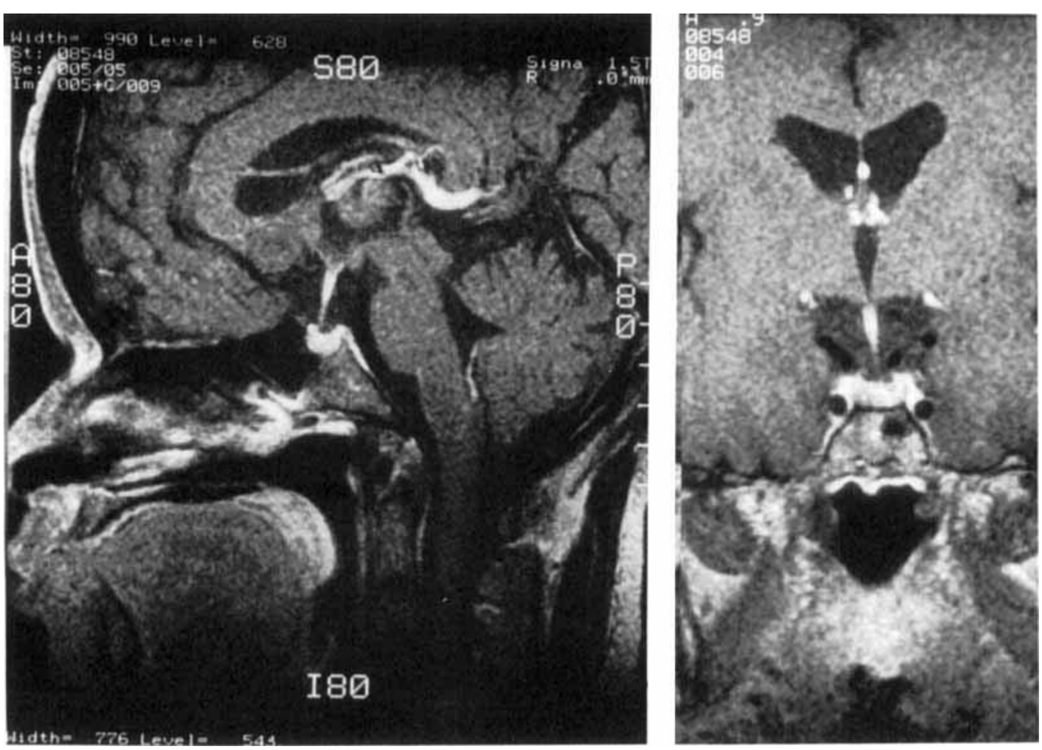

Fig. 7. Gd-DTPA enhanced MRI of sagittal section **(left)** and T_1 enhanced MRI of frontal section **(right)** of the pituitary gland. Pituitary stalk is prolonged and suprasellar cistern is wide. Optic nerve is not visible. The upper part of pituitary gland is enhanced by Gd-DTPA.

bits, dysostosis of maxilla, shortening of fifth fingers and toes, syndactyly, short stature, obesity, and diabetes mellitus.

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